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Tinidazole—a new preparation for *T. vaginalis* infections
II. Clinical evaluation of treatment with a single oral dose

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The therapy of *T. vaginalis* infections was revolutionized by the discovery of metronidazole (Cosar, Julou, and Bénazet, 1959). The course recommended as standard treatment has been 200 mg. orally three times daily for 7 days (Rodin, King, Nicol, and Barrow, 1960). In a trial by Csonka (1971), it was shown that, after a single oral dose of 2 g. metronidazole (Flagyl ®), an 82 per cent. cure rate was observed compared to 94 per cent. for the standard course. With the same single-dose treatment, Morton (1972) found a recurrence rate, including re-infections, of 18 per cent. and a true cure rate of about 90 per cent. in 118 women followed-up after treatment with metronidazole. Fourteen men were also treated and followed and none had a recurrence.

Tinidazole (Fasigyn ®) has been presented as the most potent member of a new series of nitroimidazoles (Howes, Lynch, and Kivlin, 1970). Laboratory study of the effect of tinidazole on strains of *T. vaginalis* from infected patients showed a 1·3 to 8 times higher trichomonicidal effect than that of metronidazole, and the serum level after ingestion of 2 g. in a single dose was similar (Forsgren and Wallin, 1974) to that reported for metronidazole (Woodcock, 1972). Liechti (1971) reported a cure rate of 89 per cent. in 45 women treated with 150 mg. tinidazole orally three times daily for 5 days. However, there are no published reports of the effect of tinidazole in a single oral dose in *T. vaginalis* infections. In the trial to be described, this method of treatment was evaluated.

Patients and methods

The study was carried out on 126 patients (115 women and 11 men) with *T. vaginalis* infections attending the Venereology Clinic between April, 1972, and January, 1973. Patients who were pregnant and those who could not return for further visits were excluded from the study. Most of the patients (90 per cent.) were between 15 and 30 years, and 5 per cent. of them were married. 23 per cent. had a concomitant gonococcal infection. The diagnosis of *T. vaginalis* was based on a positive culture result, but the organism was also seen in wet vaginal smears in 91 per cent. of the women. Treatment was given to women without waiting for the cultural confirmation. Symptoms possibly related to *Trichomonas* infection were recorded.

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The patients were divided into two groups:

GROUP I 68 patients were requested not to eat anything during the 4 to 5 hours before they were given 1·6 g. tinidazole (4 tablets of 400 mg.) in a single dose under supervision. They were asked to return after 1 week and again after about 1 month for further cultures. White blood cell counts and transaminase estimations were performed before the administration of the drug and again after one week when the patient had been fasting for 5 hours.

GROUP II 58 patients were given 2 g. tinidazole (4 tablets of 500 mg.) without any restrictions on food intake. They were followed up as above.

Treatment was also given to 40 per cent. of the sexual partners in both groups by providing the patient with 150 mg. tablets of tinidazole for the partner to take twice daily for 1 week.

Diagnosis

Trichomonas vaginalis was isolated within 5 days by culture in Diamond's medium incubated at 37°C. (Diamond, 1957) after using Diamond's or Stuart's medium for transport (Wallin, Gnarpe, and Forsgren, 1974). In all female cases, microscopical examination for trichomonads of wet smears of vaginal discharge was also made within 5 minutes after the collection of the specimen (Eddie, 1968). Although moist urethral scrapings were examined in male cases, most of the infections were detected only by culture.

Results

Twelve of 115 women failed to return for further examination and are excluded from the study. The remaining 103 patients attended for the first follow-up test after 4 to 21 days (mean 8 days) and 69 per cent. were also seen a second time after 3 to 15 weeks (mean 6 weeks).

Table I presents the results of treatment in 103 women. In six women recurrences were considered to be due to treatment failure and in four to re-infection after resumption of intercourse with untreated contacts. Among those given 1·6 g. tinidazole, the failure rate was 7 per cent. compared to 4 per cent. among those given 2 g. Four of the six patients who were considered to be cases of treatment failure were re-treated, two with 1·6 g. and two with 2 g. tinidazole, and one patient in each group failed a second time. The strain of *T. vaginalis* from one of the latter patients was examined for susceptibility to tinidazole and found to be sensitive.

TABLE I *Results of treatment in two groups of women based on culture findings of* T. vaginalis *before and after ingestion of tinidazole in a single dose*

Treatment (g.)	*Total no. followed*	*Probable re-infections*	*Treatment failures*	
			No.	*Per cent.*
1·6	56	4	4	7
2·0	47	0	2	4
Total	103	4	6	6

Eleven men with a *T. vaginalis* infection were treated with tinidazole in a single dose of 1·6 g. in four cases and of 2 g. in seven cases. There were no treatment failures among the ten men who completed the follow-up.

Symptoms of *T. vaginalis* infection occurred in 87 women and the effect of treatment is summarized in Table II. One week after treatment, 51 per cent. had no symptoms and 39 per cent. were improved. One patient with a concomitant and untreated gonococcal infection felt worse. The objective findings paralleled the improvement in symptoms.

TABLE II *Effect on symptoms recorded at the first visit of a single oral dose of tinidazole in two groups of women*

Effect on symptoms	*No. of women given*		*Total*
	1·6 *g.*	2·0 *g.*	
Cured	22	22	44
Improved	19	15	34
Unchanged	5	3	8
Worse	1	0	1
Total	47	40	87

Tolerance was good in both groups regardless of whether or not the drug was taken on an empty stomach. At the time of the second visit, all patients were asked about the side-effects listed in Table III. These were mentioned by 11 per cent. of the patients. Gastric discomfort occurred in three and two cases respectively in Groups I and II but none vomited.

TABLE III *Side-effects after treatment with a single oral dose of tinidazole in two groups of women*

Side-effects	*No. of women given*		*Total*
	1·6 *g.*	2·0 *g.*	
None	49	43	92
Gastric discomfort	3	2	5
Diarrhoea	2	2	4
Dizziness	2	0	2
Other	0	0	0
Total	56	47	103

White blood cell counts and transaminase levels were checked before treatment and after 1 week in 85 per cent. of the group which was given 1·6 g. tinidazole and in 82 per cent. of the group given 2 g. In the second group a differential count was also done before and after treatment. No abnormal values were found.

Discussion

The most important aetiological agent of vaginitis in adult women is *Trichomonas vaginalis* (Gray and Barnes, 1965). Epidemiological observations suggest that the disease is usually spread by sexual contact (Robinson, Mirchandani, and Causing, 1965) and many cases present for treatment in venereal diseases clinics. For more than 10 years metronidazole given for 7 days has given satisfactory results. The best way of overcoming the failure of patients to take the treatment prescribed is to give a single dose under supervision. This is also more convenient for the patient than taking two or more pills a day for 1 or 2 weeks. Single doses have for long been the preferred treatment in many clinics for patients with gonococcal infections.

Tests in the laboratory showed tinidazole to be up to eight times more active than metronidazole against strains of *T. vaginalis;* when the drug was given in a single oral dose the serum level of tinidazole remained above the trichomonicidal level for more than 48 hours (Forsgren and Wallin, 1974).

In the present study we have assessed the effect of tinidazole given in single doses. Excluding four cases of probable re-infection, the true failure rate for 99 adequately observed women was 6 per cent. The best result was obtained in the group given the higher dose (2 g. tinidazole), in which 96 per cent. of the patients were cured.

Two of the six women who were cases of treatment failure had condylomata acuminata and one had an acute endometritis. Woodcock (1972) found an apparent relationship between the failure of the 2 g. dose of metronidazole to eradicate trichomonads and the presence of undetected gonorrhoea. However, in our study, none of the six patients classed as treatment

failures had a concomitant gonococcal infection compared with a 23 per cent. incidence of gonorrhoea in the whole series. One woman treated twice with 2 g. tinidazole failed to be cured both times even though her strain of *T. vaginalis* was examined in the laboratory and found to be sensitive to tinidazole. Failure of absorption of the drug could be a possible explanation.

Although only 5 per cent. of the patients in this study were married, 40 per cent. accepted medication to be given to a sexual partner. This manner of treating the partner without examination could be a possible explanation for the low re-infection rate of only 4 per cent. in this study compared to others (Csonka, 1971; Morton, 1972). Cases recorded as re-infections could, in fact, be treatment failures, as no attempt was made to examine the sexual partners. As there were no re-infections in Group II, in which we had a cure rate of 96 per cent., this figure can be accepted without reservation.

Summary

Tinidazole, a new preparation for *Trichomonas vaginalis* infections, was given in a single oral dose of 1·6 g. to 64 women on an empty stomach, and in a single dose of 2 g. to 51 women without food restrictions. Excluding re-infections, the overall recurrence rate was 6 per cent. and, in the group given 2 g. tinidazole, 96 per cent. were cured. In three out of the six treatment failures, other concomitant genital disorders were present, but none had a gonococcal infection at the time of treatment. Ten men were also treated and followed in the same way, with no observed failures.

The treatment was well tolerated in both groups. Five patients complained of gastric discomfort but none vomited. No abnormal white blood cell counts or transaminase values were caused by the drug.

Tinidazole given in a single oral dose therefore offers a potent and practicable way of treating *Trichomonas vaginalis* infections.

References

COSAR, C., JULOU, L., and BÉNAZET, M. (1959) *Ann. Inst. Pasteur*, **96**, 238

CSONKA, G. W. (1971) *Brit. J. vener. Dis.*, **47**, 456

DIAMOND, L. S. (1957) *J. Parasitol.*, **43**, 488

EDDIE, D. A. S. (1968) *J. med. Microbiol.*, **1**, 153

FORSGREN, A., and WALLIN, J. (1974) *Brit. J. vener. Dis.*, **50**, ~~140~~ 146

GRAY, L. A., and BARNES, M. L. (1965) *Amer. J. Obstet. Gynec.*, **92**, 125

HOWES, H. L., LYNCH, J. E., and KIVLIN, J. L. (1970) 'Antimicrobial Agents and Chemotherapy—1969', ed. G. L. Hobby, p. 167. American Society for Microbiology, Bethesda, Md

LIECHTI, R. (1971) *Schweiz. Z. Gynäk Geburtsch.*, **2**, 229

MORTON, R. S. (1972) *Brit. J. vener. Dis.*, **48**, 525

ROBINSON, S. C., MIRCHANDANI, G., and CAUSING, S. (1965) *Amer. J. Obstet. Gynec.*, **91**, 1001

RODIN, P., KING, A. J., NICOL, C. S., and BARROW, J. (1960) *Brit. J. vener. Dis.*, **36**, 147

WALLIN, J., GNARPE, H., and FORSGREN, A. (1974) *Ibid.*, **50**, in press

WOODCOCK, K. R. (1972) *Ibid.*, **48**, 65

Tinidazole, une nouvelle préparation contre les infections à *T. vaginalis*
II. Résultats cliniques du traitement par une dose orale unique

SOMMAIRE

Le tinidazole, une nouvelle préparation contre les infections à *T. vaginalis*, fut donné à jeun en une dose orale unique de 1,6 g à 64 femmes, et en une dose unique de 2 g à 50 femmes ne modifiant pas leur régime. Si l'on exclut les réinfections, le taux de rechute fut dans l'ensemble de 6 pour cent et, dans le groupe recevant 2 g de tinidazole, 96 pour cent des malades furent guéries. Pour trois des échecs thérapeutiques, il existait d'autres troubles génitaux concomitants mais il n'y avait d'infection gonococcique dans acuun cas au moment du traitement. Dix hommes également furent traités et suivis de la même manière, sans que l'on observa d'échec.

Le traitement fut bien toléré dans les deux groupes. Cinq malades se plaignirent de gêne gastrique mais sans vomissements. Le médicament n'entraîna pas d'anomalie de la numération leucocytaire ni de variation des valeurs des transminases.

Le tinidazole administré en dose orale unique représente donc un moyen puissant et pratique de trasitement des infections à *T. vaginalis*.